REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

The claims have been revised so as to define the invention with additional clarity. The revisions are believed to address the Examiner's objection to claims 1 and 20. Reconsideration is requested.

Claims 1, 4-12, 20 and 22 stand rejected under 35 USC103 as allegedly being obvious over Neurath et al (EP 154902A, EP 448126A, or USP 4,847,080) Zavaglia et al and Wei et al. Withdrawal of the rejections is submitted to be in order for the reasons that follow.

The Examiner contends that it would have been obvious to one skilled in the art to combine the teachings of Wei et al with the method of Neurath et al to predict a positive response to HBV treatment from the presence of anti-preS1 antibodies, since Wei et al teaches that a patient with anti-preS1 antibodies is already on his/her way to recovery. The Examiner further contends that it would have been obvious to administer IFN to treat individuals in which preS1 antibodies were detected.

Applicants respectfully disagree and submit that an artisan could not have arrived at the claimed invention from the combined teachings of Neurath et al, Zavaglia et al and Wei et al.

The combination of Neurath et al, Zavaglia et al and Wei et al is deficient in providing no teaching or suggestion that the presence of antibodies that are specifically reactive with residues 94 to 117 of the preS1 peptide (SEQ ID NO:1) would have been predictive of a response to interferon therapy.

Neurath et al discloses the inoculation of rabbits with a preS1 (94-117) peptide (Example 10) but it is totally silent about the diagnostic or prognostic relevance of anti-preS1 (94-117)

antibodies. Neurath et al also lacks any teaching of the correlation between anti-preS1(94-117) antibodies and response to interferon therapy.

Zavaglia et al contains no teaching whatsoever about anti-preS1(94-117) antibodies.

Wei et al describes immunoassays for the detection of anti-preS1 antibodies in hepatitis B patients. However, the teachings of Wei et al do not remedy the deficiencies of Neurath et al and Zavaglia et al because those teachings relates to a different population of antibodies and do not show that the presence of this population of antibodies is predictive of response to interferon.

Wei et al relates to antibodies that bind to the 98 amino acid preS1(21-119) protein. While it includes the preS1(94-117) epitope of the pending claims, the preS1(21-119) protein also contains numerous other epitopes (e.g., 27-35, 72-78, 32-47, 41-53, 94-105, 106-117, 21-30 and 29-48: see page 276 col 2). Antibodies that bind to any of these epitopes will bind to the preS1(21-119) protein.

The experiments described in Wei et al relate to the detection of the whole population of preS1(21-119) antibodies and there is no teaching or suggestion of the detection of sub-populations that bind to the individual epitopes within the preS1(21-119) sequence.

Wei et al describes the use of ELISA to detect anti-preS1(21-119) antibodies. A positive ELISA result is observed when an antibody that binds to an epitope within the preS1(21-119) peptide is present. However, this would have provided no information about the presence of antibodies to the preS1(94-117) epitope because antibodies to other preS1(21-119) epitopes would also produce a positive result, even when antibodies to preS1(94-117) are absent.

Wei et al is therefore completely silent about antibodies to preS1(94-117) or the use of this particular sub-population as a predictive marker. This is significant because only antibodies that bind to the preS1(94-117) epitope are predictive of IFN response.

The data in the specification show that antibodies that bind to other epitopes within the pre S1(21-119) protein are not predictive of IFN response. For example, table 2b of the specification shows that 44% of non-responders have antibodies against preS1(21-32) and 56% of non-responders have antibodies against preS1(32-47). Table 3b goes on to show that 38% of non-responders have antibodies against the preS1(21-32) and 46% of nonresponders have antibodies against the preS1(32-47). Although antibodies to preS1(21-32) and preS1(32-47) would both bind the preS1(21-119) protein and, therefore, produce a positive result in the immunoassays of Wei et al, neither preS1(21-32) nor preS1(32-47) antibodies are predictive of IFN response.

It is clear from this data that the detection of preS1(21-119) antibodies using the immunoassays of Wei et al could not be used to predict the IFN response of HBV patients. Only antibodies specific for the preS1 (94-117) epitope distinguish responders from nonresponders. Wei et al lacks any teaching or suggestion regarding such antibodies, or their possible use as a predictive marker, in particular, as a predictive marker for interferon response.

This deficiency in Wei et al would not have been remedied by either Neurath or Zavaglia, which also lack any teaching or suggestion of the use of antibodies specific for preS1 (94-117) to predict the response of a patient to interferon.

Furthermore, Wei et al teaches that anti-preS1 (21-119aa) antibodies were detected in serum samples from more than half of patients with acute hepatitis B either during the acute phase (62.5%) of infection or after recovery (52.9%) (see Table 1). However, since all of the acute hepatitis B patients recovered from the infection, regardless of whether or not antibodies were present, this data does not teach, nor would it have suggested, that anti-preS1 (21-119aa)

antibodies are a predictive marker of recovery from acute hepatitis B, still less that they are predictive of the response of a patient to interferon

Anti-preS1 antibodies were hardly observed in patients with acute hepatitis B progressing to chronic disease and in chronic hepatitis patients with continuing presence of preS1 domain and seropositive of HBeAg or anti-HBe. Page 279 col 2 states:

> *In HBsAg positive individuals (Table 1), anti-preS1 antibodies were ....only found in a few of patients with chronic hepatitis,*

Consequently, Wei et al. teaches one of ordinary skill in the art that circulatory anti-preS1antibodies are very unusual in chronic patients. There is no teaching or suggestion that anti-preS1antibodies might be a marker of improvement of health in chronic patients with HBV, as alleged by the Examiner. Wei et al. followed 10 chronic patients divided in two group: one was healthy carriers with high levels of HBV DNA, preS1 antigen and HBeAg- positive (see Figure 6B), and the other was chronic hepatitis B patients with anti-HBe, low levels of HBV DNA and preS1 antigen (see Figure 6C). During the follow-up period, no anti-preS1 antibodies were detected and there was no apparent improvement in either group.

Therefore, Wei et al. would only have suggested that the absence of antipreS1 (21-119aa) is correlated to chronic HBV infection, regardless of HBeAg status. There would have been no suggestion that the presence of anti-preS1 (21-119aa) antibodies in these patients could be used as a pre-treatment marker of response to IFN-therapy.

Wei et al. also reports that anti-preS1 antibodies appeared in a few patients (the citation describes a single patient) with chronic aggressive hepatitis undergoing treatment with antiviral agents (e.g., lamivudine). The appearance of the antibodies is said to correlate well with healthy improvement (page 280 col 2). However, anti-preS1 (21-119aa) antibodies were not detected

before the treatment was initiated so the antibodies could not be used as a pretreatment marker of response to lamivudine, still less to other therapeutic agents, such as interferon.

The combination of Neurath et al, Zavaglia et al and Wei et al provides no teaching or suggestion of any prediction of responses to interferon therapy.

In summary, the combination of Neurath et al, Zavaglia et al and Wei et al would not have suggested that antibodies reactive with the preS1 peptide (94 to 117) (SEQ ID NO:1) would be predictive of a response to interferon therapy. Furthermore, this could not have been inferred from any of the cited documents, taken alone or in combination. Accordingly, reconsideration and withdrawal of the rejections are requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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